

肺血管内皮细胞在肺纤维化发病机制中的研究进展

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摘要 肺纤维化(pulmonary fibrosis, PF)是一种由过度积累的细胞外基质(extracellular matrix, ECM)引起的肺间质疾病, 可导致肺泡结构的破坏。其发病机制复杂, 涉及多种细胞类型和信号通路, 且目前尚无治愈方法。在肺纤维化的发生和发展过程中, 肺血管内皮细胞发挥着关键作用。肺血管内皮细胞可以通过内皮-间充质转化(endothelial-mesenchymal transition, EndMT)转变为肌成纤维细胞, 从而促进肺纤维化进程; 或者通过驱动炎症反应、分泌外泌体、参与血管稀疏以及血管功能障碍, 进一步推动肺纤维化的进展。因此, 靶向肺血管内皮细胞可能成为一种有效的PF治疗策略。该文将深入探讨肺血管内皮细胞在PF中的作用, 从而为PF治疗策略的制定提供帮助。

关键词 肺纤维化; 肺血管内皮细胞; 发病机制

Research Progress of Pulmonary Vascular Endothelial Cells in the Pathogenesis of Pulmonary Fibrosis

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Abstract PF (pulmonary fibrosis) is a lung interstitial disease characterized by excessive ECM (extracellular matrix) accumulation, leading to alveolar damage. Its pathogenesis is complex, involving various cell types and signaling pathways, and no cure currently exists. Lung vascular endothelial cells play a critical role in the initiation and progression of PF. These cells can undergo EndMT (endothelial-mesenchymal transition) to become myofibroblasts, promoting fibrosis, or they can drive inflammation, secrete exosomes, contribute to vascular rarefaction, and cause vascular dysfunction, further advancing the disease. Targeting lung vascular endothelial cells may thus offer a promising therapeutic approach for PF. This review will examine the role of endothelial cells in PF, providing insights for more effective treatment strategies for patients.

Keywords pulmonary fibrosis; pulmonary vascular endothelial cell; pathogenesis

肺纤维化(pulmonary fibrosis, PF)是一种进行性、不可逆且致命的肺部疾病, 目前尚无有效的治疗方法, 其主要特征为肺组织的瘢痕形成^[1]。PF是由于肺泡和血管损伤后, 肺泡上皮细胞修复失调引起的, 其

病变涉及肌成纤维细胞的增殖及细胞外基质 (extracellular matrix, ECM)的过度沉积, 导致肺部结构的变形以及肺功能的丧失^[2]。研究表明, 循环纤维细胞、肺泡上皮细胞、成纤维细胞、周细胞、巨噬细胞和

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内皮细胞均为肌成纤维细胞的前体,并共同促进了PF的发展^[3]。尽管肌成纤维细胞被认为是纤维化的核心参与者,但肺血管内皮细胞在PF中的作用近年来逐渐受到重视,内皮细胞占肺细胞总组成的30%,且研究已证实,肺血管内皮细胞的丧失和血管生成的失调是肺纤维化的重要生物学过程,因此内皮细胞在PF的发病机制中具有重要地位^[4-6]。由于内皮和肺泡上皮之间的解剖位置紧密,肺泡受损会导致血管损伤,而受损的内皮细胞可分泌促纤维化介质,并通过内皮-间充质转化(endothelial-mesenchymal transition, EndMT)迁移到肺实质区域成为致病性肌成纤维细胞;另外内皮细胞还可通过炎症反应促进免疫细胞的招募,参与血管稀疏和血管功能障碍,或通过分泌外泌体调节肺纤维化^[7-9]。然而与其他细胞类型相比,关于肺血管内皮细胞及其在PF中的作用的研究相对滞后。因此本文综述了肺血管内皮细胞对PF的贡献,这可能为进一步理解肺血管内皮细胞在PF中的作用及其发病机制提供新的思路,并探讨了靶向内皮细胞在PF治疗中的潜在应用价值,为靶向干预提供理论依据。

1 肺血管内皮细胞

肺部由支气管循环和肺循环两个血液循环系统供血,支气管循环作为体循环的一部分,是一个高压、低容量的系统,主要负责向肺组织输送氧气并处理代谢废物。相对而言,肺循环则是一个低压、高容量的系统,为肺泡内的气体交换提供了大面积的表面^[10]。肺血管系统包括动脉、毛细血管和静脉,其内壁由一层内皮细胞构成^[11-12]。在肺中表面活性物质、肺泡上皮、基膜和血管内皮细胞共同构成气血屏障,起到防止间质和肺泡水肿、确保有效气体交换的作用^[13]。肺泡毛细血管内皮细胞由两种相互交织的细胞类型构成,其中一种是肺特有的内皮细胞,参与气体交换及白细胞迁移的调控,另一种是调节血管收缩功能的一般毛细血管内皮细胞,主要在血管收缩调节、毛细血管稳态和修复中起到前体细胞的作用^[14]。有观点认为肺血管内皮在肺纤维化的发展中起着重要作用,毛细血管床及动、静脉血管中的内皮细胞网络提供了一个高度活跃的代谢屏障,控制免疫细胞的迁移,调节血管的张力和通透性,并参与血管重塑过程^[15]。在纤维化肺中,可以发现表型和功能发生改变的内皮细胞及重塑的血管^[16]。

MAGRO等^[17]在特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)患者肺活组织检查中发现有内皮微血管损伤的形态学证据,免疫荧光检测显示微血管内IgG、IgM或IgA不同程度的沉积,并在血清中检测出抗磷脂抗体阳性,这些发现说明了IPF可能是一种具有内在促血栓倾向的自身免疫性内皮炎,随后的纤维增生可被视为对免疫介导的缺氧微环境的自然细胞因子驱动的反应。另一项研究在IPF患者肺实质的受累区域发现支气管血管内皮细胞,而在正常肺中这些细胞仅限于支气管周围血管,从未在肺实质中出现,尽管目前尚不清楚肺血管内皮细胞的异位是否与IPF的发病机制相关,但这一发现强调了研究IPF肺血管内皮的重要性^[18]。

2 EndMT在肺纤维化中的作用及其调节机制

2.1 EndMT的诱因

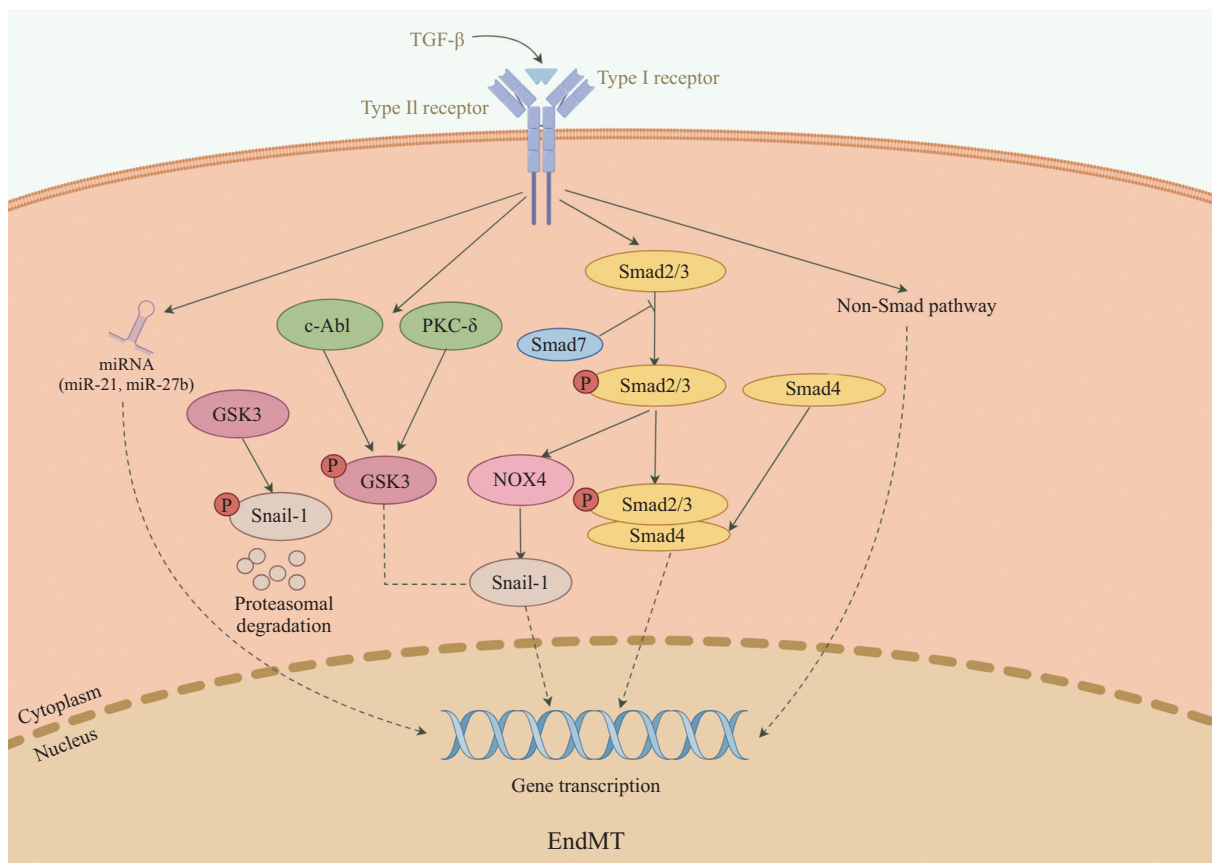
在PF过程中,内皮细胞通过EndMT成为肌成纤维细胞的来源之一,可促进纤维化进展,在此过程中肺内皮细胞脱离内皮层,形态变为细长和梭状,获得间充质表型,并呈现肌成纤维细胞分化的典型标志^[19]。在病理状态下,许多因素如缺氧、氧化应激、炎症因子和异常剪切应力等刺激均可导致内皮损伤并引发EndMT,从而导致内皮功能障碍和内环境稳态遭到破坏^[20]。(1) 一项体内研究显示,在缺氧条件下的大鼠肺血管系统中发生明显的结构重塑,表现为血管周围胶原沉积增加、血管壁增厚、管腔直径减小。体外研究也表明,缺氧条件下人肺微血管内皮细胞中间充质基因的表达水平增加,而内皮细胞标记物如CD31的表达水平降低,表明缺氧可以有效诱导EndMT^[21]。(2) 博来霉素(bleomycin, BLM)处理内皮可导致活性氧的产生,引起内皮细胞DNA应激,破坏了Wnt信号通路的平衡,从而诱导了EndMT^[22]。(3) 在炎症微环境中,EndMT的过程加剧,包括白细胞介素-1 β (interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、转化生长因子- β (transforming growth factor- β , TGF- β)等炎症因子在PF中上调,激活内皮细胞并诱导EndMT^[23]。(4) 研究发现内皮细胞中存在受剪切应力调控的转录因子KLF2,其可以促进血管生成并减少EndMT,在受到异常剪切应力时可调控内皮细胞的表型和功能^[24]。然而在BLM诱导的小鼠PF中,KLF2的表达下调^[25]。这表明,在PF的内皮细

胞中KLF2的减少促进了内皮细胞EndMT。

2.2 调节EndMT的分子机制

多种分子通路调节肺内皮细胞的EndMT过程,包括TGF- β 、骨形态发生蛋白(bone morphogenetic protein, BMP)、Notch信号转导、Wnt、内皮素-1(endothelin-1, ET-1)等^[26-27]。其大多数信号通过与TGF- β 作用来介导EndMT, TGF- β 可促进Notch与其配体结合,释放Notch胞内结构域,进而增强TGF- β 信号活性, Wnt和ET-1则协同增强TGF- β 信号,这些信号转导相互交叉影响最终激活间充质细胞特异性转录基因调控程序,导致肺内皮细胞转化为肌成纤维细胞最终促进肺纤维化^[27-29]。其中最重要的途径为TGF- β 通过激活Smad依赖性和非依赖性信号通路引起EndMT^[27]。TGF- β 结合受体后激活Smad2/3, 并与

Smad4形成复合体,促进EndMT相关基因的转录,而Smad7则可抑制此过程^[30]。Smad2/3被激活后,促进NADPH氧化酶4(NADPH oxidase 4, NOX4)的表达,进而诱导转录因子Snail-1介导的EndMT。Snail-1的活性通过糖原合成酶激酶3(glycogen synthase kinase 3, GSK3)介导的磷酸化调节, GSK3磷酸化Snail-1,促进其通过蛋白酶体降解^[27,30-32]。此外, GSK-3的活性受到c-Abl激酶和蛋白激酶C- δ (protein kinase C- δ , PKC- δ)的调控^[33]。研究表明,非编码RNA如微小RNA(microRNAs, miRNAs)在肺纤维化中也参与EndMT的调节, miR-21和miR-27b在TGF- β 诱导的EndMT中上调,抑制它们可减少EndMT的发生,进一步表明这些miRNAs在EndMT调节中发挥重要作用^[34](图1)。



EndMT的分子机制主要涉及TGF- β 与内皮细胞结合,随后激活Smad依赖性和Smad非依赖性细胞内信号通路。TGF- β 刺激NOX4的表达,导致Snail-1介导的EndMT。Snail-1是EndMT的关键调控分子,受GSK3介导的磷酸化调控,其中GSK-3的磷酸化受c-Abl激酶和PKC- δ 的调控。此外,某些非编码RNA,如miR-21和miR-27b,也在调控EndMT中发挥作用。

The molecular mechanisms of EndMT primarily involve the binding of TGF- β to endothelial cells, subsequently activating both Smad-dependent and Smad-independent intracellular signaling pathways. TGF- β stimulates the expression of NOX4, leading to Snail-1-mediated EndMT. Snail-1, a key regulator of EndMT, is modulated by GSK3-mediated phosphorylation, which is regulated by c-Abl kinase and PKC- δ . Additionally, certain non-coding RNAs, such as miR-21 and miR-27b, also play a role in the regulation of EndMT.

图1 TGF- β 诱导EndMT的分子机制(本图采用Figdraw绘制)

Fig.1 Molecular mechanism of TGF- β inducing EndMT (by Figdraw)

2.3 EndMT在肺纤维化中的作用

肺部成纤维细胞的增加及其分化为肌成纤维细胞有助于肺纤维化的进展,肌成纤维细胞通过促进ECM的产生,进一步加剧肺纤维化^[35]。在PF中,部分肌成纤维细胞来源于肺内皮细胞。HASHIMOTO等^[36]研究表明在BLM诱导的PF模型中,约有16%的肺成纤维细胞来源于肺内皮细胞。此外免疫荧光染色和单细胞测序的结果显示,在肺部纤维化区域的内皮细胞中可观察到间充质细胞标记蛋白的表达,提示这些细胞经历了EndMT过程^[37-38]。研究还发现,在放射性肺纤维化中,肺血管是最早受损的部位。小鼠模型中,肺部辐射在早期即引起血管周围胶原沉积,随后扩展到整个受照射组织^[21]。辐射诱导的缺氧在早期通过激活TGF- β 信号通路促进EndMT,从而导致血管周围胶原沉积,且这一过程发生在EndMT之前^[21,39]。鉴于EndMT是肌成纤维细胞的一个重要来源,它可能在肺纤维化的发生发展中发挥重要作用,因此靶向抑制EndMT成为肺纤维化治疗的潜在手段。最近的动物研究证实了这一观点,FU等^[40]发现,在糖尿病患者的肺组织切片中,纤维化主要积聚在肺血管周围,并伴随显著增强的EndMT,在小鼠糖尿病性肺纤维化模型中也观察到类似情况,而使用一种天然的小分子化合物芒果苷可以通过AMPK/FoxO3/SIRT3轴抑制EndMT,从而缓解了小鼠糖尿病性肺纤维化。综上所述,EndMT在PF发病机制中可能发挥关键作用。尽管许多研究通过纤维化肺组织中的内皮与间充质标志物共表达来描述EndMT,但由于EndMT是一个动态过程,且其分子机制尚未完全被阐明,仍需进一步探索,以深入理解肺纤维化机制。

3 内皮细胞驱动炎症反应在肺纤维化中的作用

内皮细胞是炎症反应的主要参与者和调节者,正常状态下内皮细胞是静止的,在损伤或病理状态下可被迅速激活,活化的内皮细胞在组织纤维化的炎症反应中起关键作用,它们通常直接引发或加剧已有的炎症反应^[6,11]。内皮细胞的激活可分为急性炎症和慢性炎症两个阶段。若急性炎症刺激持续存在,急性炎症可转变为慢性炎症,后者的特征是巨噬细胞和T细胞等白细胞的浸润。慢性炎症期间,肌成纤维细胞过度产生ECM,最终导致肺纤维化^[41-42]。

在各种致病因子引起的PF中,存在肺毛细血管

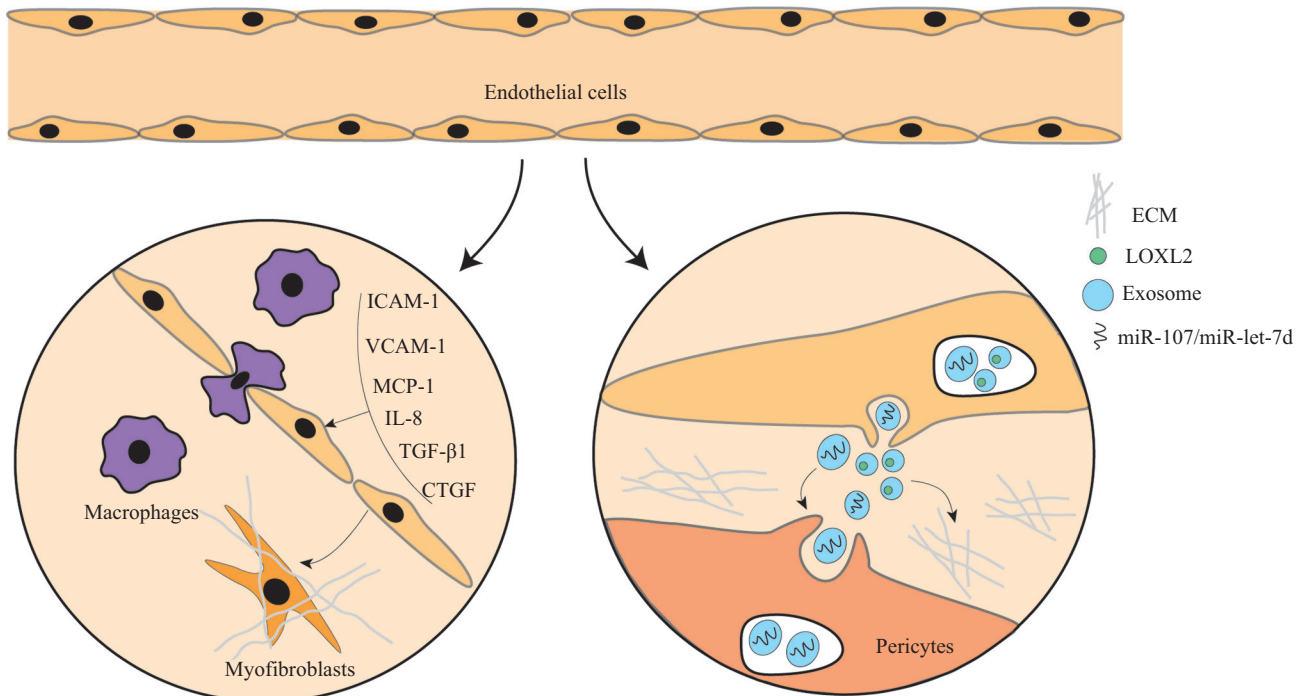
内皮细胞的损伤,从而导致促纤维化细胞因子释放,并通过释放炎症因子招募免疫细胞^[43]。WILLIAMSON等^[44]研究发现,BLM处理内皮细胞可诱导细胞间黏附分子-1(intercellular adhesion molecule-1, ICAM-1)、血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)以及单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)和IL-8等的表达,从而使肺中的免疫细胞募集,最终促进肺纤维化的发展。肺内皮细胞释放的趋化因子吸引的巨噬细胞在肺纤维化的发病机制中起着关键作用,在炎症后期阶段,M2型巨噬细胞通过分泌促纤维化因子如TGF- β 、血管内皮生长因子(vascular endothelial growth factor, VEGF)、血小板源性生长因子(platelet-derived growth factor, PDGF),加快肺纤维化进程^[45-46]。但一项对IPF肺组织内皮细胞RNA的测序研究发现,在IPF中肺内皮细胞ICAM-1表达水平降低,反映出内皮细胞介导的炎症反应受抑制,表明这可能是IPF中的一种补偿机制,用以抑制组织中的不可控炎症^[47]。YIN等^[48]研究发现,BLM处理大鼠肺微血管内皮细胞可导致内皮细胞损伤,使促纤维化细胞因子TGF- β 和结缔组织生长因子(connective tissue growth factor, CTGF)的合成和分泌上调,促进成纤维细胞向肌成纤维细胞分化并产生胶原,最终诱发肺纤维化,抗TGF- β 和抗CTGF抗体能够减少胶原合成,从而缓解纤维化。单细胞RNA测序进一步发现,内皮转录因子FOXF1在IPF患者和小鼠BLM损伤肺内皮细胞中表达下调,小鼠内皮特异性FOXF1抑制加剧胶原沉积和炎症,FOXF1缺失的内皮细胞可通过分泌IL-6、TNF- α 等因子促进肺成纤维细胞增殖、侵袭和活化,刺激巨噬细胞迁移,最终诱发纤维化^[49]。内皮细胞在肺纤维化的炎症反应中扮演重要角色,其激活可促进免疫细胞募集和促纤维化因子释放,因此,深入探讨内皮细胞在炎症与纤维化交替中的动态调节作用,可为治疗策略提供新的方向,特别是通过调控内皮细胞的特定分子和信号通路(图2)。

4 内皮细胞来源的外泌体在肺纤维化中的作用

外泌体是常见的膜结合纳米囊泡,通过胞吐作用从细胞中分泌,能够被靶细胞摄取并释放内容物(如蛋白质、脂质、核酸)到靶细胞的细胞质中^[50]。

在正常和病理条件下,肺内皮细胞均分泌功能性外泌体,参与细胞间通讯,调节凝血、炎症、凋亡、血管生成和增殖等生理过程,在多种机械、化学和分子刺激下,肺内皮细胞衍生的外泌体数量及组成均发生改变,通过影响靶细胞从而影响肺部的微环境并在肺部疾病的发病机制中发挥作用^[51-52]。有研究报道,肺部衰老内皮细胞来源的外泌体含有miR-31、miR-21和miR-217等促衰老效应因子,可以诱导其他正常细胞的早衰,并通过传播细胞衰老引发并发症,例如IPF^[53]。在缺氧及高糖的条件下,内皮细胞衍生的外泌体可能含有促纤维化因子,在调节组织纤维化的过程中至关重要,DE等^[54]发现赖氨酸氧化酶样2(lysyl oxidase-like 2, LOXL2)存在于内皮细胞衍生的外泌体中,并在缺氧条件下表达上调两倍,LOXL2通过催化ECM中弹性蛋白和胶原蛋白的交联,增加ECM的刚性和机械性能,从而促进肺纤维化的进展。这提示外泌体在缺氧调控的局部ECM重塑中发挥了作用^[55]。内皮细胞产生的外泌体中也存在具有调控肺纤维化进程的miRNAs。WANG等^[56]发

现肺内皮细胞通过产生含miR-107的外泌体显著影响周细胞的纤维化表型。周细胞是类似于成纤维细胞的细胞,负责ECM的沉积,并直接促进肺纤维化,miR-107的外泌体能够抑制肺纤维化,且在临床IPF样本和BLM诱导的PF小鼠模型中,miR-107在纤维化组织中下调^[57-58]。XIE等^[59]发现来源于肺内皮细胞的外泌体中miR-let-7d可直接与肺周细胞TGF- β 受体的启动子区结合,抑制其表达,当肺血管内皮细胞miR-let-7d外泌体分泌较少时,TGF- β 信号通路被激活,最终导致肺纤维化。还有研究表明内皮细胞可以通过分泌外泌体来调节肺泡巨噬细胞亚群的免疫表型,进而介导其向促纤维化或抗纤维化方向分化,在BLM诱导的小鼠PF模型中,气管灌注内皮细胞来源的CD31⁺外泌体或CD74⁺外泌体通过调节肺泡巨噬细胞的免疫表型,缓解肺纤维化^[60]。BACHA等^[61]发现与健康人群相比,IPF患者循环中内皮细胞来源的CD62E⁺外泌体数量显著升高,且其水平还与疾病严重程度呈正相关。这提示其有潜力作为IPF的一项重要生物标志物。总之肺内皮细胞衍生的外



内皮细胞通过分泌细胞因子促进巨噬细胞募集,并使巨噬细胞极化为M2巨噬细胞调节肺纤维化,内皮细胞激活成纤维细胞产生ECM;内皮细胞通过分泌外泌体在ECM重塑中发挥作用并调节周细胞纤维化表型。

Endothelial cells regulate pulmonary fibrosis by secreting cytokines that promote macrophage recruitment and polarization into M2 macrophages, while also activating fibroblasts to produce ECM. Furthermore, endothelial cells contribute to ECM remodeling and modulate the fibrotic phenotype of pericytes through exosome secretion.

图2 内皮细胞在肺纤维化中的调控机制

Fig.2 The regulatory mechanisms of endothelial cells in pulmonary fibrosis

泌体不仅参与肺纤维化过程,还可能成为诊断和治疗的潜在靶点。因此深入研究外泌体在肺纤维化中的具体作用机制,尤其是其在纤维化相关基因表达调控以及免疫表型改变中的作用,将为新型诊断和治疗策略的开发提供关键线索(图2)。

5 内皮细胞参与的血管稀疏在肺纤维化中的作用

血管稀疏是指微血管密度的降低,通常伴有纤维化,较低的微血管密度与纤维化严重程度相关^[6,62]。研究发现在IPF的患者中肺泡毛细血管密度在非纤维化病变区域中显著增加,而在纤维化病变区域中相应降低^[63]。关于血管稀疏导致组织纤维化,还是组织纤维化从而导致血管稀疏这一结果,目前仍存在争议,但血管稀疏已被发现先于纤维化,血管稀疏导致血管供应不足可通过慢性缺氧导致纤维化^[64-65]。在BLM诱导的小鼠PF模型中,研究发现低氧条件下培养的肺内皮细胞会显著提高促纤维化介质(如CTGF、TGF- β 、PDGF等)的表达水平,且低氧还能诱导成纤维细胞向肌成纤维细胞分化,导致胶原生成增加,这表明缺氧在肺纤维化进展中扮演重要角色^[66]。另一项研究发现BLM处理的小鼠肺血管在早期生成活跃,逐渐达到高峰,随后血管生成功能明显减弱,且血管计数逐渐减少至小于正常,并伴随着肺组织胶原纤维沉积^[67]。因此在肺纤维化的晚期阶段总体效应是肺血管密度的降低,且这一变化与内皮细胞的改变密切相关,引起血管稀疏的因素包括炎症、血管生成生长因子的缺乏等^[68]。在IPF中的早期阶段上皮细胞损伤导致有活性的TGF- β 释放,TGF- β 可以激活内皮细胞,引起血管抑制和血管生成介质(例如VEGF)的失衡,导致内皮细胞异常增殖和凋亡,并且在IPF患者的血清中发现了一种靶向内皮细胞的抗体,能够引发微血管损伤并加速内皮细胞坏死^[17,69]。另外发现在纤维化肺中能够在稳态维护或肺损伤修复中作为前体细胞发挥作用的一般毛细血管内皮细胞数量减少,这表明内皮细胞再生能力的降低有助于持久性纤维化的形成^[14,18]。CAPORARELLO等^[70]研究表明,气道内给予老年小鼠BLM,引起了毛细血管稀少,其肺内皮细胞表现出促纤维化基因表达上调和血管稳态基因表达下调。内皮细胞中去乙酰化酶SIRT1通过其去乙酰化活性调节信号通路,维持内皮细胞的血管生成潜

能。当SIRT1功能障碍时,Notch1信号通路被激活,导致毛细血管减少并参与肺纤维化的进展。这表明,SIRT1通过抑制Notch1信号通路抑制毛细血管稀疏,并拮抗肺纤维化^[71-72]。综上所述,内皮细胞的基因表达在血管稀疏过程中发生变化,提示血管稳态的维持对于纤维化的抑制至关重要。进一步研究血管稀疏与纤维化进程之间的关系,尤其是内皮细胞的作用,将有助于揭示其在肺纤维化中的关键机制。

6 内皮细胞参与的血管功能障碍在肺纤维化中的作用

微血管功能随着年龄的增长而减弱,主要表现为血管生成能力降低,导致其修复功能受损;黏附分子表达异常,导致炎症细胞的募集;血管舒张功能受损,使毛细血管压力过大,导致蛋白质渗漏、水肿形成和组织损伤。这些因素共同推动了肺纤维化的发生^[73]。衰老相关微血管功能障碍的主要机制是氧化应激,从而导致内皮细胞功能障碍和凋亡^[74]。RASLAN等^[75]通过单细胞RNA测序研究了年轻和老年小鼠的BLM损伤肺,发现了年轻小鼠肺内皮细胞的活化状态仅在胶原生成高峰期短暂出现,而老年小鼠肺中内皮细胞活化持续存在于纤维化区域,表明老年肺血管无法恢复静止状态,并表现出内皮基因下调和炎症、纤维化基因上调,提示衰老相关的血管内皮功能障碍促进了肺纤维化进展。近来发现糖尿病病变带来的微血管功能障碍有导致肺部疾病的可能性,肺部具有丰富的血管网络,高血糖引起的肺血管功能障碍,可通过氧化应激、纤维化信号失调、慢性炎症引起肺间质的纤维化,且有证据表明糖尿病有增加IPF发病风险的可能^[76-77]。有研究发现在没有肺动脉高压的IPF患者中,观察到肺血管功能障碍,表现为肺血管阻力升高,且高的阻力与死亡率增加有关^[78]。对BLM诱导的PF小鼠内皮细胞的表观遗传学和转录分析表明,内皮转录因子ETS相关基因*ERG*通过染色质重塑调控血管修复,在衰老过程中其功能减弱,导致内皮细胞*ERG*异常,进而促进肺纤维化^[79]。此外血管分泌系统的功能障碍也与肺纤维化密切相关,例如,内皮细胞中H₂S的释放障碍导致纤溶酶原激活物抑制剂-1(plasminogen activator inhibitor-1, PAI-1)的表达上调,最终促进肺纤维化的发生^[80]。内皮细胞功能障碍目前被认

为是肺纤维化发展的一个关键因素,但现有的研究多集中于描述性分析,缺乏对内皮细胞功能障碍是否直接导致肺纤维化或仅通过影响局部环境间接加剧肺纤维化的机制的探讨,因此未来还需进一步研究验证。

7 小结

本文总结了肺血管内皮细胞在肺纤维化发病机制中的重要作用,并探讨了其多维度的参与机制。现有研究普遍认为,肺泡上皮细胞的异常激活是纤维化反应的关键驱动因素,但具体是上皮细胞信号传递给内皮细胞引发纤维化过程,还是内皮细胞本身在纤维化的起始阶段扮演主导角色,这一问题仍然存在争议。因此,尽管肺血管内皮细胞在肺纤维化中的潜在作用已引起广泛关注,但其具体机制仍需进一步深入研究。肺血管内皮细胞通过多种途径参与了肺纤维化的发生发展,这些作用不仅涉及内皮细胞本身,还包括其与其他细胞类型的相互作用。因此未来的研究还应聚焦于内皮细胞与其他细胞类型之间的相互作用与协同机制,以揭示其在纤维化进程中的多层次作用,这将为肺纤维化的治疗提供更加全面和有效的理论支持。

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